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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/873,797	06/04/2001	Nnochiri N. Ekwuribe	9233.63	2859

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 02/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/873,797	EKWURIBE ET AL.	
	Examiner	Art Unit	
	Jeffr y E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-103* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-24,26-38,40-46,48-62,64-82 and 84-103* is/are rejected.

7)☒ Claim(s) *12,25,39,47,63 and 83* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 June 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/15/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The sequence listing filed June 6, 2003 has been approved.

2. The drawings are objected to because in Figure 42 (y-axis label) and Figure 43 (right-hand side), "LUCIFERASE" is misspelled. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

3. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

4. Claims 2, 3, 13, 14, 51, 71, and 74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 2, 3, 13, and 14 are indefinite because it is not clear what are the lower limits to the ranges specified in the claims. For example, with respect to claim 2, assuming that "at least 2" is the lower limit to the number of PEG subunits, it is at best redundant to state that greater numbers of PEG subunits may be present. Assuming that 3 or 4 is intended to be the lower limit to the claimed ranges, then it is contradictory to also recite "at least 2". Claims 3, 13, and 14 are indefinite for analogous reasons. There is no antecedent basis in the claims for the phrase "the second polyethylene glycol moiety" at claim 51, line 2. It is possible that claim 51 should instead depend upon claim 50; however, claim 50 recites a second polyalkylene glycol moiety rather than a second polyethylene glycol moiety. There is no antecedent basis in the claims for the phrase "the oligomer" at claim 71, line 1, and claim 74, line 1. Note that independent claim 65 uses the terminology "polymer" rather than "oligomer".

5. Claims 85-88, 91, 92, and 94 are objected to because of the following informalities: At claim 85, line 12, the semicolon after "moiety" should be changed to a comma, and the comma after "m is 1" should be changed to a semicolon. Appropriate correction is required.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-11, 13-24, 26-38, 40-46, 52-62, 64-73, 75-82, 84-89, 91, 92, and 94 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 103-122 of copending Application No. 09/873,757. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '757 application anticipate instant claims 1, 5, 6, 13-19, 26-33, 40, 41, 52-56, 64-67, 75, 76, 84, 85, and 94. Because the structures and homogeneity of the conjugates are the same, the claimed conjugate mixtures of the '757 application would have been expected to have the same greater in vivo and in vitro activity, the same increased resistance to degradation by chymotrypsin, the same lesser inter-subject variability, and the same amphiphilic balance as is recited in instant claims 26-29 and 52. With respect to instant claims 7-11, 20-24, 34-38, 42-46, 57-62, 68-73, 77-82, 86-89, 91, and 92, while the '757 application does not claim a polyalkylene glycol which is polyethylene glycol or polypropylene glycol, it would have been obvious to one

of ordinary skill in the art to form the claimed conjugates of the '757 application using polyethylene glycol or polypropylene glycol as the polyalkylene glycol because these are the two most common polyalkylene glycols used in the conjugate arts. With respect to instant claims 2-4, 58, 69, 78, and 87, while the '757 application does not claim a size for its polyalkylene glycols, it would have been obvious to one of ordinary skill in the art to determine all operable and optimal polyalkylene glycol sizes for the conjugates claimed in the '757 application because polymer size is an art-recognized result-effective variable which is routinely determined and optimized in the conjugate and polymer arts.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 1-11, 13-24, 26-38, 40-46, 48-62, 64-73, 75-82, and 84-103 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-10, 15, 17, 19, 21, 23-26, 28-32, 42-46, 48-52, 54-57, 64-71, 73-135 of copending Application No. 09/873,777. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '777 application anticipate instant claims 1-9, 13-22, 26-36, 40-44, 48-60, 64-71, 75-80, 84-90, and 94-103. Because the structures and homogeneity of the conjugates are the same, the claimed conjugate mixtures of the '757 application would have been expected to have the same greater in vivo and in vitro activity, the same increased resistance to degradation by chymotrypsin, and the same lesser inter-subject variability as is recited in instant claims 26-29. With respect to instant claims 10, 11, 23, 24, 37, 38, 45, 46, 61, 62, 72, 73, 81, 82, and 91-93, while the '757 application does not claim a polyalkylene glycol which is polyethylene glycol or polypropylene glycol, it would

have been obvious to one of ordinary skill in the art to form the claimed conjugates of the '757 application using polyethylene glycol or polypropylene glycol as the polyalkylene glycol because these are the two most common polyalkylene glycols used in the conjugate arts.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Claims 1-9, 13-22, 26-36, 40-44, 48-60, 64-71, 75-80, 84-90, and 94 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 7-11, 16-30, 40, 41, 46-48, 50, 52, and 68-102 of copending Application No. 09/873,899. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '899 application anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

11. Claims 1-9, 13-22, 26-36, 40-44, 48, 49, 51-60, 64-71, 75-80, 84-89, and 94 are rejected under 35 U.S.C. 103(a) as being obvious over Clark (U.S. Patent No. 5,597,797) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. Clark teaches preferably 2-8 polyethylene glycol molecules having a molecular weight of 5,000 - 40,000 preferably conjugated to epsilon-amino groups of lysine residues present in human growth hormone. The polyethylene glycol can be substituted with a C1-C4 alkyl. See, e.g., column 5, lines 45-57; column 10, lines 11-56; and column 13, lines 34-39. Clark does not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. The PEG can be

monomethoxyPEG. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application '740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. The polyethylene glycol can be capped at one terminus of methyl. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; page 11, lines 8-12; and page 15, lines 1-5. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the PEG-growth hormone conjugates of Clark using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by Clark; because the use of discrete length PEG in the conjugates of Clark would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

12. Claims 1-9, 13-22, 26-36, 40-44, 48, 49, 51-60, 64-71, 75-80, 84-89, and 94 are rejected under 35 U.S.C. 103(a) as being obvious over Cunningham et al (U.S. Patent No. 6,057,292) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. Cunningham et al teach preferably about 4-6 polyethylene glycol molecules having a molecular weight of 4,000 - 20,000 preferably conjugated to epsilon-amino groups of lysine residues present in human growth hormone. One end of the polyethylene glycol can be blocked with

methoxy in order to prevent crosslinking. The conjugates are used, e.g., to treat growth hormone deficiency and to accelerate growth of humans. See, e.g., column 20, line 53 - column 21, line 67; column 23, lines 45-55; column 25, lines 11-39; and column 27, lines 2-20. Cunningham et al do not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. The PEG can be monomethoxyPEG. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application '740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. The polyethylene glycol can be capped at one terminus of methyl. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; page 11, lines 8-12, and page 15, lines 1-5. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the PEG-growth hormone conjugates of Cunningham et al using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by Cunningham et al; because the use of discrete length PEG in the conjugates of Cunningham et al would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado would have been expected to

have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

13. Claims 1-9, 13-22, 26-36, 40-44, 48, 49, 51-60, 64-71, 75-80, 84-89, and 94 are rejected under 35 U.S.C. 103(a) as being obvious over Ekwuribe (U.S. Patent No. 5,359,030) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. Ekwuribe teaches conjugates in which a polymer comprising a PEG moiety which preferably has more than 7 subunits and a lipophilic moiety is conjugated via a labile bond to a peptide, which can be somatotropin (i.e. growth hormone), calcitonin, or insulin, and which conjugation can occur at an amine group present on the peptide. Plural polymers can be conjugated to each peptide. Conjugation results in prolonged blood circulation and enhanced resistance to enzymatic degradation, relative to the peptide alone. See, e.g., the Abstract; column 6, lines 41-61; column 11, line 20; column 12, lines 11-16 and 35-40; column 13, Conjugates 2 and 3; and column 14, lines 3-14 and 43-55. While Ekwuribe does not teach using somatotropin-based conjugates to treat growth hormone deficiency or to accelerate the growth rate of an animal, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use the somatotropin-based conjugates of Ekwuribe for these purposes because the treatment of growth hormone deficiency and the acceleration or growth rate are primary uses of somatotropin. Ekwuribe does not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. The PEG can be monomethoxyPEG. See, e.g., the Abstract; column 6, lines 19-41;

and claims 1-9. The WO Patent Application 97/14740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. The polyethylene glycol can be capped at one terminus of methyl. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; page 11, lines 8-12, and page 15, lines 1-5. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the somatotropin conjugates of Ekwuribe using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by Ekwuribe; because the use of discrete length PEG in the conjugates of Ekwuribe would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

14. Claims 1-9, 13-22, 26-36, 40-44, 48, 49, 51-60, 64-71, 75-80, 84-89, and 94 are rejected under 35 U.S.C. 103(a) as being obvious over Ekwuribe (U.S. Patent No. 5,359,030) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740 as applied against claims 1-9, 13-22, 26-36, 40-44, 48, 49, 51-60, 64-71, 75-80, 84-89, and 94 above, and further in view of the Harris et al article (J. Macromol., Sci., Vol. C25, pages 325-373). Ekwuribe does not teach the number or the size of the oligomers which are to be conjugated to each somatotropin molecule. The Harris et al article teaches that when using PEG-protein

conjugates, the degree of substitution and PEG molecular weight should be optimized in order to achieve the protein's desired effect (see, e.g., page 351, first full paragraph). Accordingly, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to optimize result-effective conjugate properties, e.g., degree of substitution and polymer size, as taught by the Harris et al article for the PEG-somatotropin conjugates of Ekwuribe in order to maximize the conjugates' desirable properties.

15. Claims 1-9, 13-22, 26-31, 33-36, 40-44, 48, 49, 51-60, 64-71, 75-80, 84-89, and 94 are rejected under 35 U.S.C. 103(a) as being obvious over the European Patent Application 0 511 903 in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. The European Patent Application '903 teaches methoxy-polyethylene glycol having a molecular weight of 500-20,000 conjugated to the carboxylic group of human, salmon, or eel calcitonin via formation of an amide bond. The conjugates are used to treat osteoporosis, hypercalcaemia, and Paget's disease. See, e.g., the Abstract. While the European Patent Application '903 does not teach the degree to which the conjugates are able to lower serum calcium levels, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to optimize result-effective conjugate properties, e.g., degree of substitution and polymer size, in order to maximize its conjugates' desirable properties. While the European Patent Application '903 does not teach that conjugation increases resistance to chymotrypsin degradation and increases bioefficacy, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made that the conjugation of the European Patent Application '903 would have these results because it is well-known in the art, as shown by the WO Patent Application '740 at page 2, lines 3-13, that PEG conjugation to proteins

decreases in vivo proteolysis and increases in vivo half-lives of the proteins compared to their unconjugated state. The European Patent Application '903 does not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application '740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the PEG-calcitonin conjugates of the European Patent Application '903 using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by the European Patent Application '903; because the use of discrete length PEG in the conjugates of the European Patent Application '903 would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

16. Claims 1-9, 13-22, 26-31, 33-36, 40-44, 48, 49, 51-60, 64-71, 75-80, 84-89, and 94 are

rejected under 35 U.S.C. 103(a) as being obvious over the European Patent Application 0 511 903 in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740 as applied against claims 1-9, 13-22, 26-31, 33-36, 40-44, 48, 49, 51-60, 64-71, 75-80, 84-89, and 94 above, and further in view of the Harris et al article (J. Macromol., Sci., Vol. C25, pages 325-373). As noted above, while the European Patent Application '903 does not teach degree to which the conjugate is able to lower serum calcium levels, the Harris et al article teaches that when using PEG-protein conjugates, the degree of substitution and PEG molecular weight should be optimized in order to achieve the protein's desired effect (see, e.g., page 351, first full paragraph). Accordingly, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to optimize result-effective conjugate properties, e.g., degree of substitution and polymer size, as taught by the Harris et al article for the PEG-calcitonin conjugates of the European Patent Application '740 in order to maximize the conjugate's desirable properties.

17. Claims 1-9, 13-22, 26-36, 40-44, 52-60, 64-71, 75-80, 84-89, and 94 are rejected under 35 U.S.C. 103(a) as being obvious over the Hinds et al article (Bioconj. Chem., Vol. 11, pages 195-201) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. The Hinds et al article teaches methoxy-polyethylene glycol having a molecular weight of 750 or 2,000 daltons conjugated to the amino group of either the PheB1 or LysB29 residues of human insulin. The conjugates are expected to have increased plasma half-lives, reduced immunogenicity and antigenicity, and improved resistance to proteolysis, and are used to treat insulin-dependent diabetes. See, e.g., the Abstract; page 195, column 1, first paragraph; and page 196, column 1, first and second full paragraphs. The Hinds et al article does not teach

monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application '740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the PEG-insulin conjugates of the Hinds et al article using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by the Hinds et al article; because the use of discrete length PEG in the conjugates of the Hinds et al article would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado et al would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

18. Claims 1-9, 13-22, 26-36, 40-44, 52-60, 64-71, 75-80, 84-89, and 94 are rejected under 35 U.S.C. 103(a) as being obvious over Liu et al (U.S. Patent No. 6,323,311) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. Liu et al teach

oligomers comprising polyethylene glycol conjugated to the PheB1 residue of human insulin. The polyethylene glycol can comprise from about 3 to about 400 PEG subunits. The oligomers can also comprise lipophilic moieties (see, e.g., claims 13 and 18, in which the $(CH_2)_p$, $(CH_2)_r$, $(CH_2)_m$, $(CH_2)_k$ groups correspond to Applicants' lipophilic moieties). The conjugates have increased stability, increased mean residence time, and attenuated immunogenicity and antigenicity. See, e.g., the Abstract; column 2, lines 35-39; column 6, lines 4-21 and 33-35; Example 1; and column 8, lines 11-19. Liu et al do not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application '740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the PEG-insulin conjugates of Liu et al using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by Liu et al; because the use of discrete length PEG in the conjugates of Liu et al would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as

taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado et al would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

19. Claims 1-9, 13-22, 26-36, 40-44, 52-60, 64-71, 75-80, 84-90, 94, 95, 99, and 101-103 are rejected under 35 U.S.C. 102(e) as being anticipated by Ekwuribe et al (U.S. Pub. No. 2003/0050228). Ekwuribe et al '228 teaches and claims monodispersed mixtures of an insulin drug-oligomer conjugate where the oligomer is $C(=O)-(CH_2)_5-(OC_2H_4)_7-OCH_3$ attached to LysB29 (see, e.g., claims 170, 183, and 186). Ekwuribe et al '228 synthesizes the monodispersed oligomers by the same method claimed by Applicants (see, e.g., Figures 14 and 15). Ekwuribe et al '228 is prior art against the instant claims because its disclosure of the monodispersed mixtures is supported by the disclosure of the provisional application upon which it claims priority (see, e.g., page 9, lines 21-27, and Figures 14 and 15 of provisional application 60/269,198) and because the inventorship of Ekwuribe et al '228 is different than the inventorship of the instant application.

20. Claims 1-9, 13-22, 26-36, 40-44, 52-60, 64-71, 75-80, 84-89, and 94 are rejected under 35 U.S.C. 103(a) as being obvious over the Radha Krishnan et al article (Proceed. Int'l. Symp. Control. Rel. Bioact. Mater., Vol. 27, pages 1038-1039) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. The Radha Krishnan et al article teaches methoxy-polyethylene glycol having 7±3 subunits conjugated through hexanoic acid to the amino group of the LysB29 residue of human insulin. The conjugates are orally active and thermally stable. See, e.g., Figure 1 and page 1039, column 2, last paragraph. The Radha Krishnan et al article does not teach monodispersed conjugate mixtures with low molecular

weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application '740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the PEG-Hex-insulin conjugates of the Radha Krishnan et al article using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by the Radha Krishnan et al article; because the use of discrete length PEG in the conjugates of the Radha Krishnan et al article would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado et al would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

21. Claims 1-9, 13-22, 26-36, 40-44, 52-60, 64-71, 75-80, 84-89, and 94 are rejected under 35 U.S.C. 103(a) as being obvious over the Radha Krishnan et al article (Proceed. Int'l. Symp. Control. Rel. Bioact. Mater., Vol. 27, pages 1038-1039) in view of Delgado et al (U.S. Patent

No. 5,349,052) and the WO Patent Application 97/14740 as applied against claims 1-9, 13-22, 26-36, 40-44, 52-60, 64-71, 75-80, 84-89, and 94 above, and further in view of the Harris et al article (J. Macromol. Sci., Vol. C25, pages 325-373). As noted above, while the Radha Krishnan et al article does not teach the polymer size for insulin conjugates in particular, the Harris et al article teaches that when using PEG-protein conjugates, PEG molecular weight should be optimized in order to achieve the protein's desired effect (see, e.g., page 351, first full paragraph). Accordingly, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to optimize result-effective conjugate properties, e.g., polymer size, as taught by the Harris et al article for the PEG-insulin conjugates of the Radha Krishnan et al article in order to maximize the conjugates' desirable properties.

22. Claims 1-9, 13-22, 26-36, 40-44, 52-60, 64-71, 75-80, 84-89, and 94 are rejected under 35 U.S.C. 103(a) as being obvious over the Radha Krishnan et al abstract (1999 Nat. Meet. Amer. Assoc. Pharm. Scient.) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740. The Radha Krishnan et al abstract teaches methoxy-polyethylene glycol having n subunits conjugated through hexanoic acid to the amino group of the LysB29 residue of human insulin. The conjugates are orally active, are enzymatically stable, and have improved amphiphilic characteristics and lower aggregation. The Radha Krishnan et al abstract does not teach PEG having seven subunits (i.e., n=7), and does not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-

41; and claims 1-9. The WO Patent Application '740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal PEG sizes for the PEG component taught by the Radha Krishnan et al abstract because polymer size is an art-recognized result-effective variable which is routinely determined and optimized in the polymer arts, and because Delgado et al teach the desirability of optimizing PEG length in order to isolate the specific conjugate possessing optimal biological properties. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to prepare the PEG-Hex-insulin conjugates of the Radha Krishnan et al abstract using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of the WO Patent Application '740 is an available source of the PEG required by the Radha Krishnan et al abstract; because the use of discrete length PEG in the conjugates of the Radha Krishnan et al abstract would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado et al would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties.

23. Claims 1-9, 13-22, 26-36, 40-44, 52-60, 64-71, 75-80, 84-89, and 94 are rejected under

35 U.S.C. 103(a) as being obvious over the Radha Krishnan et al abstract (1999 Nat. Meet. Amer. Assoc. Pharm. Scient.) in view of Delgado et al (U.S. Patent No. 5,349,052) and the WO Patent Application 97/14740 as applied against claims 1-9, 13-22, 26-36, 40-44, 52-60, 64-71, 75-80, 84-89, and 94 above, and further in view of the Harris et al article (J. Macromol. Sci., Vol. C25, pages 325-373). As noted above, while the Radha Krishnan et al abstract does not teach the polymer size for insulin conjugates in particular, the Harris et al article teaches that when using PEG-protein conjugates, PEG molecular weight should be optimized in order to achieve the protein's desired effect (see, e.g., page 351, first full paragraph). Accordingly, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to optimize result-effective conjugate properties, e.g., polymer size, as taught by the Harris et al article for the PEG-insulin conjugates of the Radha Krishnan et al abstract in order to maximize the conjugates' desirable properties.

24. Claims 76-80 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 97,14740. The WO Patent Application '740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12.

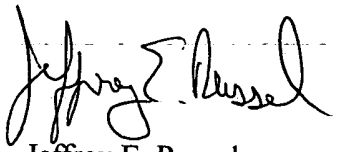
25. Claims 12, 25, 39, 47, 63, and 83 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 74 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. The prior art of

record does not teach or suggest a drug conjugated to an oligomer comprising polypropylene glycol moiety and devoid of a lipophilic moiety, where the conjugate is in substantially monodispersed form or has a molecular weight distribution with a standard deviation of less than about 22 Daltons or has a dispersity coefficient greater than 10,000 or has the same number of polypropylene glycol subunits. Note that the prior art such as Delgado et al (U.S. Patent No. 5,349,052) or the WO Patent Application 97/14740 does not teach or suggest how to make polypropylene glycol which satisfies Applicants' claimed molecular weight distribution or dispersity limitations. The disclosures of Delgado et al and the WO Patent Application '740 are limited to polyethylene glycol, and their syntheses and purifications do not necessarily extrapolate to polypropylene glycol.

The Coudert et al article (Synth. Comm., Vol. 16, pages 19-26) has been carefully considered, but does not teach or suggest the use of a mesylate activating group in reacting its ethylene glycol subunits with one another (see page 20).

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (571) 272-0961. The fax number for Technology Center 1600 for formal communications is (703) 872-9306; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (703) 308-0196.



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January 31, 2004